REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendment and remarks. No new subject matter or new issues of patentability is introduced in this amendment. Entry of this amendment is respectfully requested. It is believed that entry of the amendment places the application into condition for allowance.

Claims 33-49 are pending in the instant application.

35 U.S.C. §112 REJECTION

Claim 33 has been rejected under 35 U.S.C. §112, first paragraph. The Examiner asserts that the phrase "unmodified probe" is not supported in the originally filed specification and that no "evidence that this phrase has a well known and fixed definition in the art" has been provided. Applicants respectfully disagree with this rejection.

The term "unmodified probe" is commonly understood by those skilled in the art to be a nucleic acid, which is not chemically or structurally changed from what is understood in the art to be a nucleic acid, and which is used as a probe. According to Webster's Third New International Dictionary of the English Language Unabridged (Philip Babcock Gove, Ph.D. Merriam-Webster, Inc., Springfield, MA, 1993), "unmodified" is defined as not modified. "Modify" is defined as: to make minor changes in the form or structure of; and to change the form or properties of for a definite purpose. One skilled in the art understands the meaning of "unmodified probe" as a nucleic acid molecule not having any changes in its form, structure, or properties. According to the American Heritage Dictionary, a "probe" in biology is defined as a "substance such as DNA, that is radioactively labeled or otherwise marked and used to detect or identify another substance in a sample" (The American Heritage Dictionary® of the English Language: Fourth Edition. 2000). Furthermore, the term "label" is chemically defined as a "tracer, which is an identifiable substance, such as a dye or a radioactive isotope." Thus, the term "unmodified probe" is commonly known and understood and has a fixed definition in the art.

There are several means for labeling nucleic acids or probes as illustrated in the enclosed publication by Deborah Stull (*The Scientist* 15(10): 20, May 14, 2001) submitted

herewith for the Examiner's convenience. The nick translation, random priming, and enzymatic labeling methods described in this article all modify or incorporate a label in the DNA. Thus, the skilled artisan reading this article and the instant specification understands the meaning of "unmodified nucleic acid probe" as being a nucleic acid that has not been altered or modified structurally or chemically.

The Examiner admits that "the specification as originally filed teaches the use of labeled and unlabeled probes," but contends that the "specification does not discuss the concept of modifying probes and does not disclose the specific embodiment of unmodified probes" (Paper 10, pg.2). Applicants respectfully disagree with the Examiner's contention.

With respect to the issue of whether the specification as originally filed provides a basis for the concept of unmodified probes, applicants respectfully direct the Examiner's attention to page 10, paragraph 38 of the instant specification which describes unlabeled or unmodified probes and mixture of probes that are preferred. Pages 13-14 (Conjugation of Anti-hybrid Antibody) describes detecting the RNA probe/ DNA hybrid by labeling anti-hybrid antibodies. Although, probes "can also be prepared so that they are linked to detectable labels" (pg. 10, lns. 13-15), one skilled in the art understands that the probes are preferably unlabeled. Thus, one reading the instant description understands the meaning of an unmodified probe to be a nucleic acid substance that does not have any changes in form, structure or properties thereof, and that may nevertheless detect or identify another substance in a sample.

In addition, the method of modifying probes is commonly known and understood in the art and further discussed in the Background section of the instant specification under "Hybridization Probes" (pgs. 1-3). The Examiner's attention is respectfully directed to the Examples section, specifically Examples 1, 2, and 4-6 which describe the non-radioactive hybridization assay of the present invention using unmodified RNA probes. In particular, Example 1 compares the present invention using unmodified probes to a radioactive method (ViraType™ HPV detection kit) using modified probes. Therefore, applicants have described modifying probes and the use of both modified and unmodified probes as described in the Examples section. Therefore, applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

Claims 33 and 43-45 have been rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully disagree with this rejection.

The Examiner has rejected claim 33 under §112, second paragraph as being indefinite for the recitation of the term "unmodified" probes and argues that "there is no art recognized definition for what constitutes an unmodified probe." For the reasons discussed above, applicants respectfully disagree with this position. Furthermore, the Examiner's attention is respectfully directed to the MPEP 2173.05(e) under "A claim term which has no antecedent basis in the disclosure is not necessarily indefinite." The MPEP states :

> The mere fact that a term or phrase used in the claim has no antecedent basis in the specification disclosure does not mean, necessarily, that the term or phrase is indefinite. There is no requirement that the words in the claim must match those used in the specification disclosure. (MPEP, page 2100-200; Eighth edition; emphasis added).

Since the MPEP states that the exact term or phrase used in the claim is not required in the specification, the instant specification need only define "unmodified probe" in a manner that one skilled in the art would understand, although a specification need not be burdened with subject matter well-known in the art. A skilled artisan, looking at a nucleic acid structure can immediately recognize nucleic acids which are unmodified as compared to those whose structure has been modified and contain an altered chemistry and/or structure. Modifications necessary for detection or attachment to a solid matrix are clearly modifications not necessary for the present invention, because the probes of the present invention are neither attached to a matrix nor detectably labeled. For these reasons, applicants believe that the phrase "unmodified nucleic acid probes" is not indefinite. Reconsideration and withdrawal of this §112 rejection is respectfully requested.

35 U.S.C. §103 REJECTION

Claim 33 has been rejected under 35 U.S.C. §103(a) as being obvious over Rashtchian. Applicants respectfully disagree with this rejection.

Rashtchian describe the use of a biotinylated probe and a streptavidin conjugated peroxidase to detect the complex. In fact, on page 1526, col. 2 ("Materials" section), of the Rashtchian publication, the probes were synthesized and terminated with an amino propyl-

modified cytidine analog and then biotinylated. The Examiner argues that because the term "unmodified" is considered to be indefinite, the biotinylated probe of Rashtchian's assay is believed to be included in the claim. Any skilled artisan would recognize that a biotin attached to a nucleic acid is a modification of the chemical and structural integrity of a nucleic acid. There are many ways by which a molecule may be biotinylated, *i.e.*, amines, thiols, aldehydes, and carboxyls. Biotins may be conjugated to a nucleic acid by 5' terminal end labeling. This method of labeling nucleic acids incorporates a biotin, for example, into the phosphate nucleic acid molecule. Thus, the nucleic acid probe of Rashtchian is a modified nucleic acid probe, as defined above and as is well known in the art. Therefore, the modified probe of Rashtchian does not obviate applicants' unmodified nucleic acid probe. Reconsideration and withdrawal of this §103(a) rejection is respectfully requested.

Claims 33-36 have been rejected under 35 U.S.C. §103(a) as obvious over Rashtchian in view of Carrico. Applicants respectfully disagree with this rejection.

As previously discussed, Rashtchian describes an assay which uses a biotin modified nucleic acid probe. This is because biotinylation alters the chemical and structural integrity of any nucleic acid.

The Examiner contends that although Carrico uses a probe that is immobilized, this does not imply that the probe is modified. However, as previously described, an "unmodified nucleic acid probe" is a nucleic acid that has not been altered or modified, physically, structurally or chemically. Carrico uses a modified probe, in that the probe described by Carrico must be physically immobilized or immobilizable (through a modification of the probe nucleic acid) onto a solid matrix so that the target nucleic acid may be separated from the sample. Carrico's probe in the first example is first immobilized and then used in a solid phase hybridization step. The immobilization of the probe alters its physical properties (*i.e.*, its ability to diffuse in an aqueous solution). However, these immobilization and solid phase hybridization steps are not carried out in the subject of the instant invention. The second example presented by Carrico utilizes a modified probe introduced into a solution phase hybridization step. Carrico teaches how the probe must be modified in order to render the probe immobilizable in this embodiment. *See, e.g.*, col. 7, lns. 19-20, which states that the "the probe and the sequence of

interest are rendered immobilized through a property of the probe." In fact, cols. 7-8 further describe various ways of modifying RNA or DNA probes for immobilizing the probe to a solid surface, *i.e.*, through phosphate groups activated by carbodimimide or carbonyldiimidazole (col. 7, lns. 65-67); guanine and thymidine residues of the polynucleotide (col. 8, lns. 2-4); and phosphodiester links between the terminal phosphate of the polynucleotide and the support hydroxyls (col. 8, lns. 6-10). All of the examples of Carrico describe use of an immobilized RNA or DNA probe. Therefore, one reading Carrico would understand that the immobilized probes of Carrico are physically or chemically modified.

Applicants' probe is NOT modified or directly immobilized to a solid surface as that suggested by Carrico. As claimed, an anti-hybrid antibody or functional anti-hybrid antibody fragment is immobilized. The double-stranded RNA:DNA hybrid, formed by the sample nucleic acid sequence hybridized to a complementary unmodified nucleic acid probe, is captured by the immobilized anti-hybrid antibody. Therefore, one skilled in the art from reading Carrico and Rashtchian would have no guidance or motivation to combine the two publications in order to obtain the invention of the instant application.

The teachings of Rashtchian combined with Carrico do not make obvious the present invention. Rashtchian detects the complex directly from a labeled probe, while Carrico immobilizes the complex using a immobilized or immobilizable probe. Neither Rashtchian nor Carrico teaches or suggests that a completely unmodified probe may be used in an assay, where antibodies both sequester and detect a target complex without directly immobilizing the probe. Additionally, neither of these references suggests how one skilled in the art would be capable of immobilizing and detecting a target complex without first modifying and/or immobilizing the probe used in the assay. For all of the above reasons, applicants submit that the combination of Rashchian and Carrico do not teach or suggest the claimed invention and therefore, do not render claims 33-36 obvious. Therefore, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4023.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2629-4023. A DUPLICATE OF THIS SHEET IS ATTACHED.

Respectfully submitted,

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Dated: April 11, 2003

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